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Dated 4 July 2003

Patents Form 1/77

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17 JUN 2002
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1/77

18JUN02 E726438-4 D02890
P01/7700 0.00-0213869.1

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
South Wales
NP9 1RH

1. Your reference — REP07147GB

2. Patent application number *(The Patent Office will fill in this part)* — 17 JUN 2002 — 0213869.1

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

   Arakis Ltd.
   Chesterford Research Park
   Little Chesterford
   Saffron Walden
   Essex CB10 1XL

   08306128001
   Patents ADP number *(if you know it)*

   If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention — THE TREATMENT OF PAIN

5. Name of your agent *(if you have one)* — Gill Jennings & Every

   "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

   Broadgate House
   7 Eldon Street
   London
   EC2M 7LH

   Patents ADP number *(if you know it)* — 745002 ✓

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

   a) any applicant named in part 3 is not an inventor, or
   b) there is an inventor who is not named as an applicant, or
   c) any named applicant is a corporate body.
   See note (d))

   YES

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	3
Claim(s)	1
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	NO

11. For the applicant
Gill Jennings & Every

I/We request the grant of a patent on the basis of this application.

Signature

Date
17 June 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

R E Perry
020 7377 1377

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.*

b) *Write your answers in capital letters using black ink or you may type them.*

c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*

d) *If you have answered 'Yes' Patents Form 7/77 will need to be filed.*

e) *Once you have filled in the form you must remember to sign and date it.*

f) *For details of the fee and ways to pay please contact the Patent Office.*

THE TREATMENT OF PAIN

Field of the Invention

This invention relates to the treatment of pain.

Background of the Invention

Nefopam [(±)-3,4,5,6-tetrahydro-5-methyl-1-phenyl-1H-2,5-benzoxazocine hydrochloride] is a centrally acting non-narcotic analgesic not structurally related to other analgesics. Nefopam has been shown to induce antinociception in animal models of pain and in humans (reviewed in Heel *et al.*, 1980). However, nefopam is not active in the mouse tail-flick test, or the hot plate test and the Randall-Selitto pressure test in rats (Conway and Mitchell, 1977), suggesting that its analgesic mechanism is not opiate-like or anti-inflammatory in nature. Nefopam's antinociception is not blocked by nalaxone, further suggesting that its analgesic action is not through opiate receptors. Although the precise mechanism of antinociception is not known it is thought to involve inhibition of synaptosomal uptake of dopamine, norepinephrine and serotonin (VonVoigtlander *et al.*, 1983; Rosland and Hole, 1990; Mather *et al.*, 2001).

In vitro and *in vivo* studies with nefopam enantiomers have shown that (+)-nefopam has more potent analgesic and dopamine, norepinephrine and serotonin-uptake inhibitory properties than (-)-nefopam, with the order of potency given as (+)-nefopam > (±)-nefopam > (-)-nefopam (Fasmer *et al.*, 1987; Rosland and Hole, 1990; Mather *et al.*, 2001). Mather *et al.* (2001) conclude that "...there is currently no compelling rationale to justify administering or monitoring individual enantiomers [of nefopam]".

Nefopam has also been shown to be opiate-sparing when given with morphine in trials of patient-controlled analgesia (Mimoz *et al.*, 2001).

Conventional release preparations of nefopam have been commercially available for many years for use in moderate to severe pain yet the short elimination half-life of nefopam (four hours) means that it is difficult to maintain analgesic efficacy over the normal dosing period (three times daily). Dose escalation of nefopam brings about an increase in the frequency of adverse drug reactions associated with the analgesic, and adverse effects on pulse and blood pressure have been observed following parenteral delivery of therapeutic doses

of nefopam (Heel *et al.*, 1980). Chronotropic and ionotropic effects on the heart are not present when nefopam is administered orally (Bhatt *et al.*, 1981).

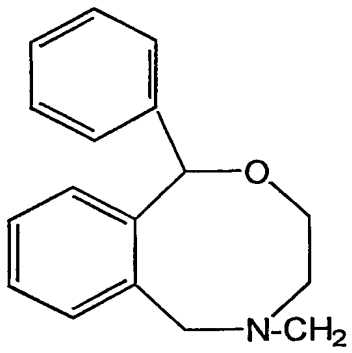
Despite nefopam's long-standing use, controlled release preparations for oral administration containing nefopam as active ingredient have not previously been described.

Summary of the Invention

According to the present invention, emesis or pain such as acute, chronic or neuropathic pain (including, but not limited to, pain associated with cancer, surgery, arthritis, dental surgery, painful neuropathies, trauma, musculo-skeletal injury or disease, visceral diseases) and migraine headache in mammals, can be treated by the use of nefopam. This can be done using nefopam or another analgesic drug in (a) an immediate release form in association with nefopam in (b) a controlled release form.

Description of Preferred Embodiments

Nefopam has formula I



(I)

The compound expressed by the formula includes (+) and (-) enantiomers and the (+) isomer (nefopam) is preferably used.

Preferably, the immediate release analgesic drug is an opioid analgesic. An alternative preference is that the immediate release analgesic drug is at least one of acetaminophen, a non-steroidal anti-inflammatory drug, a narcotic analgesic, a local anaesthetic, an NMDA antagonist, a neuroleptic agent, an anti-convulsant, an anti-spasmodic, an anti-depressant or a muscle relaxant.

Preferably, the component (b) is co-administered with (c) an analgesic

amount of an opiate, the total amount of (b) and (c) administered being a more effective analgesic. Alternatively, the component (b) is co-administered with (c) an analgesic amount of at least one nefopam analgesia-enhancer selected from acetaminophen, a non-steroidal anti-inflammatory drug, a narcotic analgesic, a local anaesthetic, an NMDA antagonist, a neuroleptic agent, an anti-convulsant, an anti-spasmodic, an anti-depressant and a muscle relaxant, the total amount of (b) and (c) administered being a more effective analgesic.

Another preference is that component (b) is co-administered with (c) a nefopam analgesia-enhancing, but essentially sub-analgesic, amount of an opiate analgesic, the total amount of (b) and (c) administered being an effective analgesic. Another alternative preference is that component (b) is co-administered with (c) a nefopam analgesia-enhancing, but essentially sub-analgesic, amount of at least one nefopam analgesia-enhancer selected from acetaminophen, a non-steroidal anti-inflammatory drug, a narcotic analgesic, a local anaesthetic, an NMDA antagonist, a neuroleptic agent, an anti-convulsant, an anti-spasmodic, an anti-depressant, a muscle relaxant, the total amount of (b) and (c) administered being an effective analgesic.

Another aspect of the invention is where nefopam is used to treat emesis, including, but not limited to, acute, delayed, post-operative, last-phase, and anticipatory emesis, for example, induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorder, motion, post-operative sickness, surgery, gastrointestinal obstruction, reduced gastrointestinal motility, visceral pain, migraine, opioid analgesics and variations.

Any suitable route of administration can be used. For example, any of oral, topical, ocular, rectal, vaginal, inhalation and intranasal delivery routes may be suitable.

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Any suitable route of administration can be used. For example, any of oral, topical, ocular, rectal, vaginal, inhalation and intranasal delivery routes may be suitable.

CLAIMS

1. Use of nefopam or an enantiomer thereof for the manufacture of a medicament for use in the treatment of pain.

2. Use of nefopam or an enantiomer thereof for the manufacture of a medicament for use in the treatment of emesis.